

REMARKS/ARGUMENTS

I. Status of the Claims. Claims 1-14 are pending. Claims 4 and 7-12 have been withdrawn from consideration by the Examiner as being directed to non-elected subject matter.

Claim 1 has been amended to remove extraneous parentheses. The amendments to claim 1 are editorial in nature and do not change the scope of claim 1. Nor are they made for any reason substantially related to patentability.

By this Amendment, no new matter has been added to the application.

II. Claim Rejections. The rejections set out in the Final Office Action are summarized and addressed as follows.

(i) Rejection Under 35 U.S.C. §103(a). Claims 1-3, 5, 6 and 13 remain rejected as allegedly obvious over Umeda et al., U.S. Patent No. 6,342,516 (“the ‘516 patent”) in view of Hansch et al., Substituent Constants for Correlation Analysis in Chemistry and Biology, (1979), Wiley, pp. 1-63 (“Hansch”). The rejection is respectfully traversed on the grounds that the state of the art does not support modifying the ‘516 patent to arrive at the claimed invention and, further, because the claimed invention provides unexpected results over the prior art.

The rejection is first traversed on the grounds that the Examiner has failed to make out the required *prima facie* case that the elected species set forth in claim 14 is obvious over compound 3-19 of the ‘516 patent in view of the teachings of Hansch. In *Eisai Co. Ltd. v. Dr. Reddy's Laboratory*, 533 F.3d 1353 (Fed. Cir. 2008), the Federal Circuit considered obviousness in the context of chemical compounds. The court noted where chemical compounds are concerned, an obviousness analysis “often turns on the structural similarities and differences between the claimed compound and the prior art compounds.” *Id.* at 1356-57, citing *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006). The court stated:

Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.

Id. at 1357, citing *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). A finding of obviousness is supported when “the claimed and prior art compounds possess a ‘sufficiently close relationship . . . to create an expectation,’ in light of the totality of the prior art, that the new compound will have ‘similar properties’ to the old.” Quoting *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007), quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*). As noted by the court, in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) the Supreme Court set forth that “obvious to try” could support a finding of obviousness “[w]hen there [was] . . . a design need or market pressure to solve a problem and there [were] . . . a finite number of identified, predictable solutions.” *Id.* at 1742. The “obvious to try” standard, however, “relies on several assumptions,” *viz.*: (i) “a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions,” (ii) a presupposition “that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound” (citing *Takeda*, 492 F.3d at 1357); and (iii) “that the record before the time of invention would supply some reasons for narrowing the prior art universe to a “finite number of identified, predictable solutions.” *Eisai Co. Ltd.*, 533 F.3d at 1359, citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. at 1742. The court cautioned that:

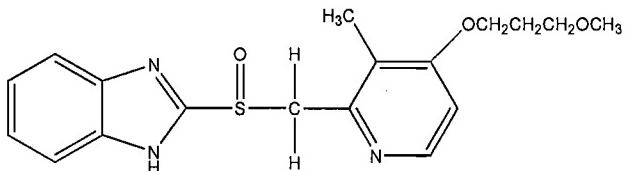
To the extent an art is unpredictable, as the chemical arts often are, KSR’s focus on these “identified, predictable solutions” may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Id. The court concluded:

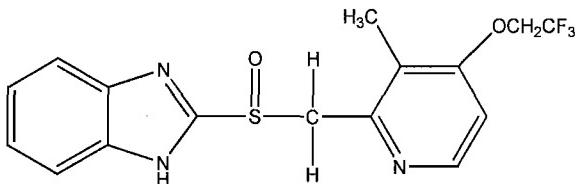
In other words, *post-KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.

Id.

In *Eisai Co. Ltd.*, the Federal Circuit applied the principles set out above to the question of whether the compound rabeprazole was obvious over the prior art compound, lansoprazole. Rabeprazole has the structure:



Lansoprazole has the structure:



Thus, difference between the prior art compound and the claimed compound was the replacement of the trifluoroethoxy substituent present in the prior art compound with a methoxypropoxy substituent. *Id.* at 1357 (structures in original). As in the instant case, the difference between the prior art compound and the claimed compound is a single side chain on an aromatic ring. The Federal Circuit upheld the district court's summary judgment ruling that rabeprazole was not obvious over lansoprazole, based on the finding that when the prior art was taken as a whole there was no reason to choose lansoprazole for a lead compound as a starting point to develop new gastric acid inhibitors. *Id.* at 1358-1359.

The salient facts in the instant case are similar to those found in *Eisai Co. Ltd.* In both instances, the difference between the prior art and the claimed compound is a substitution of a single substituent on an aromatic with another substituent that was known in the prior. As in *Eisai Co. Ltd.*, the assertion of obviousness must first fail because there was no rationale for choosing compound 3-19 of the '516 patent as a starting point or lead compound. Thus, compound 3-19 is only one of over 1000 compounds set out Tables 1-4 of the '516 patent. The '515 patent does not offer any benefit or advantage to choosing compound 3-19 over all of the other compounds set out therein. Thus, the scope and content of the prior art does not include a rationale for basing an obvious rejection on compound 3-19.

Moreover, even if there were a reason to choose compound 3-19 from the '516 patent (which Applicants believe not to be the case), there would still be no reason to choose among the 166 "well-characterized aromatic substituents" set out in Hansch. In *KSR*, the Supreme Court stated

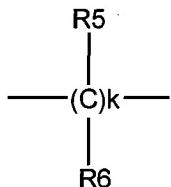
that “obvious to try” is a permissible grounds for an obviousness rejection when the prior art offers a choice among a “finite number of identified, predictable solutions.” *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct at 1742. Here, the ‘516 patent discloses over 1000 compounds as possible starting points for compounds with anti-oxidant activity without offering any reason to choose one or another of them and Hansch discloses 166 “well-characterized aromatic substituents,” each of which might serve equally well as substituent on the compounds set out in the ‘516 patent. In particular, there is no suggestion in Hansch that an amino group could or should be substituted for an acetoxy group. Thus, the Examiner has applied an “obvious to try standard” where the prior art offers over 166,000 possible solutions to finding additional compounds with anti-oxidant activity. Applicants submit this large number of possibilities is clearly outside the bounds of the “finite number of identified, predictable solutions” envisioned by the Supreme Court in *KSR*.

In short, in contrast to the guidance of the Federal Circuit and the Supreme Court, in the instant case, the totality of the prior art (i) fails to provide a reference point or points from which a skilled artisan can identify a problem and pursue potential solutions; (ii) fails to give some reason to make particular modifications to achieve the claimed compound; and (iii) fails to provide a reason “for narrowing the prior art universe to a ‘finite number of identified, predictable solutions.’” For at least these reasons, the rejection of claims 1-3, 5, 6 and 13 as obvious over the ‘516 patent in view of Hansch should be withdrawn.

The non-obviousness of the instant claims is further supported by the attached Declaration of co-inventor Seiichi Uchida. The Uchida Declaration reports on the results of experiments designed to compare the antioxidative activities of elected compound 37 and the prior art compound 3-19 when administered orally to male SD rats at a dose of 30 mg/kg. The Uchida Declaration reports that administration of compound 37 inhibited the level of ex vivo lipid peroxide action in the brain by $55 \pm 7.9\%$, versus an inhibition level of $19 \pm 10.3\%$ observed following administration of compound 3-19. The Uchida Declaration concludes that compound 37 exhibits significantly enhanced antioxidative action in the brain, compared to compound 3-19. The results reported in the Uchida Declaration are objective evidence that the instant claims are not obvious over the prior art of record. For this reason additionally, the rejection of the claims as obvious over the ‘516 patent in view of Hansch should be withdrawn.

For all of the reasons set forth above, the rejection of claims 1-3, 5, 6, 13 and 14 should be withdrawn. Reconsideration of the claims and withdrawal of the rejection based on the '516 patent and Hansch is respectfully requested.

(ii) Rejection Under 35 U.S.C. §112, first paragraph (written description). The Examiner asserts that claim 14 includes new matter because it recites a subgenus of claim 1 that does not have support in the specification. The Examiner's assertion is based on the position that claim 14 does not recite compound 37, as was intended, because variable B is not defined. The Examiner position, however, is not well taken, as follows. Claim 1 sets forth that variable B represents the formula

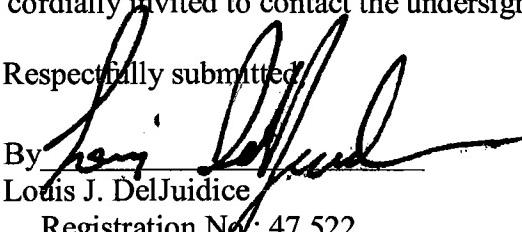


and that variable "k" represents 0 or an integer of 1 to 15. Claim 14 calls for variable k to be 0 (zero). Variable B is thus defined in claim 14 to be a bond (or, alternatively stated, as absent). In short, claim 14 specifically recites compound 37. The basis for the instant rejection is thus mistaken. Withdrawal of the rejection of claim 14 for alleged introduction of new matter is respectfully requested.

III. Conclusion. This application is believed to be in condition for allowance, which is earnestly solicited. If the Examiner believes there are remaining issues that could be addressed by an Examiner's Amendment, he is cordially invited to contact the undersigned attorney.

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Respectfully submitted,

By 
Louis J. DelJuidice

Registration No.: 47,522
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)

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Attorneys/Agents For Applicant